PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ON/4 -33227A/USN	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/EP2004/006317	International filing date *(day/month/year)* 11.06.2004	Priority date *(day/month/year)* 13.06.2003
International Patent Classification (IPC) or national classification and IPC A61K31/505, C07D239/42, C07D401/04, C07D401/14, C07D403/04, C07D417/04, A61K31/506, A61P35/00		
Applicant NOVARTIS AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand 11.01.2005	Date of completion of this report 30.06.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Telephone No. +49 89 2399- 8274 Garrido, D.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/006317

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-55 as originally filed

   Claims, Numbers

   1-34 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/006317

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-34
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-34
Industrial applicability (IA)	Yes:	Claims	1-25, 31-34
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 26-30 relate to subject-matter considered by this Authority to be covered by the provision of Rule 67.1(iv)PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claims(article 34(4)(a)(I)PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. **Reference is made to the following documents**

D1: ZIMMERMANN J ET AL: "Phenylamino-pyrimidine (PAP) - derivatives: a new class of potent and highly selective PDGF-receptor autophosphorylation inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 6, no. 11, 4 June 1996 (1996-06-04), pages 1221-1226, XP004134858 ISSN: 0960-894X

D2: WO 02/22597 A (NOVARTIS ERFIND VERWALT GMBH ; BREITENSTEIN WERNER (CH); CARAVATTI GIO) 21 March 2002 (2002-03-21)

D3: WO 02/093164 A (AXXIMA PHARMACEUTICALS AG ; BACHER GERALD (DE); MUELLER STEFAN (DE); S) 21 November 2002 (2002-11-21)

D4: US-B-6 180 6311 (KUTSCHER BERNHARD ET AL) 30 January 2001 (2001-01-30)

D5: WO 03/022833 (SMITHKLINE BEECHAM PLC) 20 March 2003

2. **Novelty** (article 33(1) and (2)PCT)

The present application describes compounds of formula(I) (see present claim 1), wherein R1 is a phenyl or heteroaryl radical and R2 is a phenyl radical, the above-mentioned moieties can be substituted or not (see description page 3-paragraph 6).

D4-D5 disclosed RAF inhibitors which present a completely other core-structure, therefore they are disregarded for the assessments of the novelty of the present subject-matter.

The 2-pyrimidyl derivatives 3-7, 13-14 disclosed by D1 (see scheme 1 and table 1) are novelty destroying embodiments for the present claimed compounds (see present Claim 1), The general formulae claimed by Claims 4-7 of D2 present overlapping regions with the present claimed formula (I) (claim 1). Moreover, the examples 1-16 disclosed by D2 are novelty-destroying embodiments for the present claimed general structure (I). D3 disclose compounds of formula (I) (see Claim 1), which present an overlapping region with the present claimed compounds of formula (I), when R is methyl, Z is NHCOX(see Claims 1 and 6 of D3 and present Claim 1). Moreover, the examples 8, 16, 17, 18, 21, 22, 29, 30, 32, 34, 36, 37, 39, 46, 51-53, 55-56, 78, 81 and 82 are novelty-destroying embodiments for the present claimed structure (I). The (4-pyridin-2yl-pyrimidin-2yl-)amine as the corresponding 4-pyridin-3-yl and 4-pyridin-4-yl amine disclosed by D3 (see Claim 3 of D3 when Z is NH2) are novelty destroying for the subject-matter claimed by the present Claim 33. Consequently, the novelty of compounds of formula (I) claimed by the present Claim 1 cannot be acknowledged.

3. **Inventive step** (Article 33(1) and (3)PCT)

Since, the documents D1-D3 disclose compounds and general formulae which are either novelty destroying embodiments or present overlapping regions with the present general structure (I), an inventive step can be discussed only for the compounds which are novel over the cited prior art documents (e.g. compounds of formulae II-V).

The present application describes compounds of formula (I) for which R1 is a phenyl or heteroaryl moiety and R2 is a phenyl moiety as RAF kinase inhibitors and therefore useful to treat proliferative diseases.

D2, which can be regarded as being the closest prior art, disclosed compounds which differ from the present compounds of formulae (II-V) only through the substitution of present R1 moiety (see present structures II-V and the examples of D2). The compounds disclosed by D2 are also useful in treatment of proliferative diseases and moreover they can act in the Map kinase pathway (see D2 -page 6-paragraph 3). It appears to be irrelevant that D1-D3 do not disclose specifically the RAF kinase affinity of 2-amino-pyrimidyl derivatives, since it refer to the same use in terms of disorders to be treated (proliferative diseases). The possible discovery of a specific mechanism cannot be taken as an objective problem and

eventually an inventive step as such. As it was shown, the compounds of D1-D3, are appropriate to treat exactly the same diseases as the compounds of the present application. Since it is not clear from the present application in comparison with the prior art compounds that other diseases could be treated with the present compounds, the prior art compounds should be considered as technically equivalent with the present compounds. Consequently, no inventive step can be acknowledged for the present subject-matter as it is not yet shown by appropriate information, e.g. in form of experimental data, either that substantially all the claimed compounds have un unexpected property or improved activity over the structurally closest prior art compounds, which is attributable to the distinguishing feature of the invention or that other not disclosed disease by the prior art can be treated by the present compounds.